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(19)(CA) **CANADIAN PATENT** (12)

(54) 13 α-Alkylgonanes, their Preparation and Pharmaceutical Preparations Containing them

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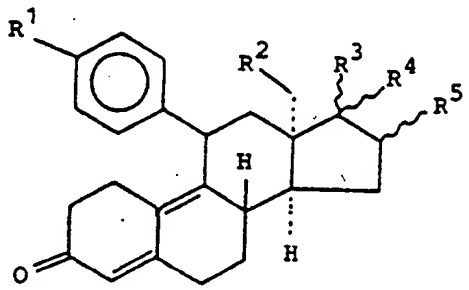
NO DRAWING

13α-alkylgonanes, their preparation and pharmaceutical preparations containing them

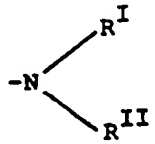
The present invention provides 13α-alkylgonanes of the general formula



(I)

in which

R^1 represents

a group of the general formula  in which

R^I and R^{II}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, or

R^I and R^{II}, together with the nitrogen atom to which they are attached, represent a saturated 5- or 6-membered ring, which may, if desired, contain a further hetero atom, or

X *

OR^{III} in which

R^{III} represents a methyl, ethyl, propyl, isopropyl, methoxyphenyl, allyl or β-dimethylaminoethyl group,

R^2 represents a hydrogen atom, a methyl group or an ethyl group,

R^3 represents a group of the general formula $-(CH_2)_n-CH_3$ in which

n represents 0 or an integer from 1 to 4, a group of the general formula $-(CH_2)_n-CH_2-OR^{IV}$ or $-(CH_2)_n-CH_2-SR^{IV}$ in which

n represents 0 or an integer from 1 to 5, and

R^{IV} represents a hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms,

a group of the general formula $-CH=CH-(CH_2)_n-OR^V$ in which

n represents an integer from 1 to 4, and

R^V represents a hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms,

a group of the general formula $-C\equiv C-X$ in which

X represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms or a halogen atom,

X

a group of the general formula $-(CH_2)_n-CH_2CH$ in which

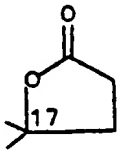
n represents 0 or an integer from 1 to 3, or

a group of the formula $-\overset{O}{\overset{\|}{C}}-CH_2Y$ in which

Y represents a hydrogen atom of a group of the general formula OR^V in which R^V has the meaning given above,

R^4 represents a hydroxy group or an alkoxy or alkanoyloxy radical each having from 1 to 4 carbon atoms or

R^3 and R^4, together with the carbon atom to which they are attached, represents a group of the formula



and R^3 is in the α-configuration and R^4 is in the β-configuration or R^3 is in the β-configuration and R^4 is in the α-configuration with respect to the steroid structure,

and

R^5 represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms and being in the α-or β-configuration,

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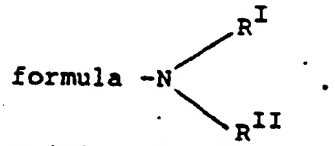
and the corresponding tertiary N-oxides and physiologically tolerable acid addition salts, of such compounds in which R^1 represents a group of the general



These compounds have a strong affinity for the gestagen receptor without themselves having gestagenic activity. They are competitive antagonists of progesterone (antigestagens) and are suitable for inducing abortions since they expel from the receptor the progesterone necessary to maintain pregnancy. The compounds are therefore valuable and interesting with regard to their use for postcoital (p.c.) fertility control.

Corresponding compounds in the oestrane series have already been described as antigestagenically active compounds in Fertility and Sterility 40 (1982), page 253.

The structure-action relationships known hitherto for competitive progesterone antagonists indicate that a 1,3-diaxial arrangement of an 11β-aryl radical and a 13β-alkyl group are absolutely necessary for the development of antigestagenic activity. All the more surprising, therefore, is the strong and selective antagonistic action of the 13α-alkylgonanes of the general formula I which has a completely different molecular topography from the oestrane series.

An alkyl radical represented by R^I and/or R^{II} has from 1 to 4 carbon atoms, the methyl group and the ethyl group being preferred. Preferably R^I and R^{II} are the same.

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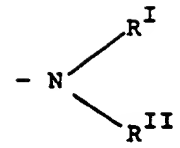
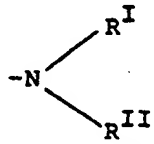
The group  may also represent a saturated 5- or 6-membered ring which, apart from carbon atoms and the nitrogen atom shown may also contain a further hetero atom, such, for example, as O, N or S; examples of such groups are the pyrrolidino, piperidino, piperazino, morpholino, oxazolidino and thiazolidino and thiadiazolidino rings.

The  radical may also be in the form of a tertiary N-oxide, such as, for example, dimethylamino-N-oxide, and pyrrolidino-, piperidino-, piperazino-, morpholino-, oxazolidino-, thiadiazolidino and thiazolidino-N-oxide.

An alkyl radical represented by X and/or R^5, an alkyl or alkanoyl radical represented by R^{IV} or R^V and an alkoxy or alkanoyloxy radical represented by R^4 each has from 1 to 4 carbon atoms; methyl, ethyl, acetyl and propionyl are preferred.

The following groups should especially be mentioned:

for R^1: $N(CH_3)_2$, $N(C_2H_5)_2$, OCH_3,
for R^2: H, CH_3,
for R^3: $C{\equiv}CH$, $C{\equiv}CCH_3$, CH_2CH_2OH, $CH{=}CHCH_2OH$, CH_2CN and $COCH_3$,
for R^4: OH and, especially when R^3 represents $COCH_3$, $OCOCH_3$,
for R^5: H, C_2H_5.

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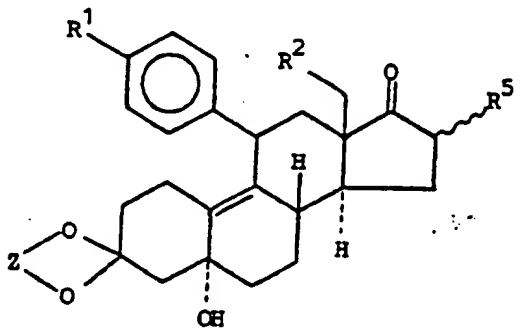
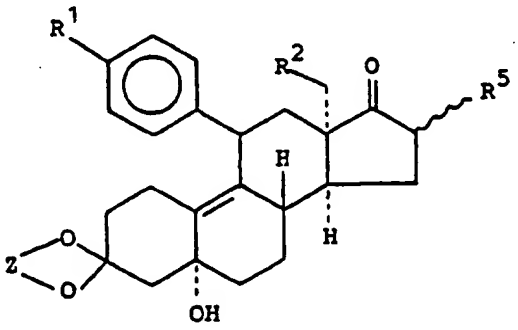
A 13α-alkylgonane of the general formula I or N-oxide or acid addition salt thereof may be prepared by irradiating a compound of the general formula



(II),

in which R^1, R^2 and R^5 have the meanings given above and Z represents an ethylene or 2,2-dimethylpropylene group, or other ketone-protecting group, or an N-oxide or acid addition salt thereof, with ultraviolet light, and converting the resulting 13-epi-steroid of the general formula



(III),

in which R^1, R^2, R^5 and Z have the meanings given above, or an N-oxide or acid addition salt thereof into a compound of the general formula I, for example by a method known per se by nucleophilic addition to the 17-ketone group, cleavage of

X

the 3-ketal protection and the splitting off of water from the 4,5-position.

The present invention provides a process for the preparation of a compound of the general formula I or an N-oxide or salt thereof from a compound of the general formula II or N-oxide or salt thereof by the process described above.

The present invention also provides a process for the preparation of a compound of the general formula I or an N-oxide or salt thereof from a compound of the general formula III or N-oxide or salt thereof by the steps of nucleophilic addition to the 17-ketone group, cleavage of the 3-ketal protecting group and the splitting off of water from the 4,5-position.

If desired, a compound of the general formula I or salt thereof may be converted to a different compound of the general formula I or salt thereof or N-oxide thereof.

Nucleophilic addition to the 17-ketone group may be performed before or after the splitting off of water; advantageously the nucleophilic addition is performed and then de-protection of the 3-ketal group and the splitting off of water are performed simultaneously.

Accordingly, the present invention further provides a process for the preparation of a compound of the general formula I, in which R^1, R^2, R^3, R^4, R^5 and Z have the meanings given above, or an N-oxide or salt thereof from a compound of the general formula

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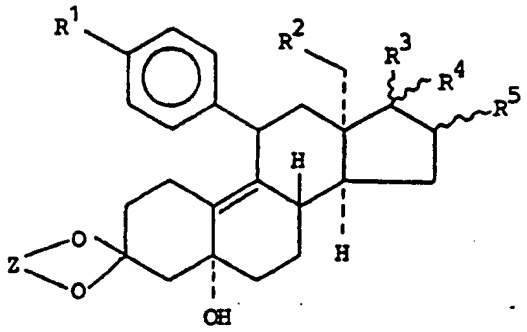
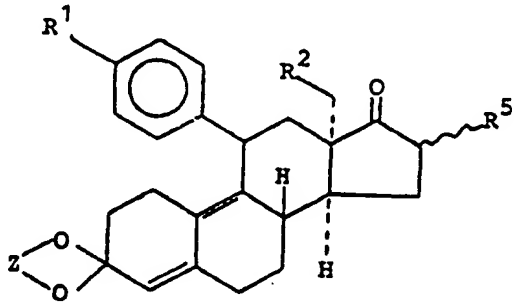


IV

or N-oxide or salt thereof, which comprises cleavage of the 3-ketone protecting group and the splitting off of water from the 4,5-position,

or from a compound of the general formula



(V)

or N-oxide or salt thereof, which comprises nucleophilic addition to the 17-ketone group and cleavage of the 3-ketal protecting group.

If desired, a compound of the general formula IV or salt thereof may be converted to a different compound of the general formula IV or salt thereof or N-oxide thereof.

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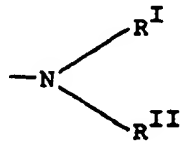
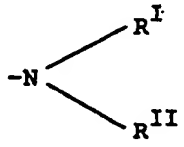
Th present invention further provides a compound of the general formula IV or an N-oxide or acid addition salt of such compound in which R^1 represents a group of the general formula



The present invention also provides a compound of the general formula V or an N-oxide or acid addition salt of such a compound in which R^1 represents a group of the general formula



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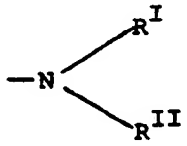
The present invention also provides a compound of the general formula III or an N-oxide or acid addition salt of such compound in which R^1 represents a group of the general formula



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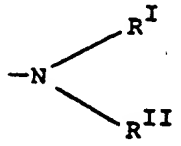
and a process for its preparation by irradiation of a compound of the general formula II or N-oxide or acid addition salt of such compound in which R^1 represents a group of the general formula



with UV light.

By irradiation with ultraviolet light, a 13β-alkyl steroid of the general formula II is converted, with a good yield, into the 13-epi-steroid (13α-alkyl steroid) of the general formula III.

The good yield of the conversion product is surprising. Although it has long been known that 17-oxo steroids of the normal series can be converted by UV irradiation into 13-epi-steroids (A. Butenandt et al., Ber. Deutsch. Chem. Ges. 74, 1308 (1941)), mixtures of the starting material and the epimerised compound were always obtained, the irradiation times were several hours and the yields were extraordinarily low. The search for an alternative chemical means of obtaining the 13-epi series is therefore still going on, as more recent work by Barton et al., J.C.S. Perkin I, 2163 (1977) shows. This alternative is, however, thought to be unsuitable for the manufacture of compounds of the general formula I. We have found that, under certain conditions, the irradiation of compounds of the general formula II (or their N-oxides or salts) is considerably more successful than in the series of 11-unsubstituted 17-oxo steroids: the average

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irradiation times are only from 10 to 30 minutes and the yields of 13-epi-steroid may be from 60 to 80 %. If desired, the irradiation products may be reacted further without chromatographic purification. Optimum results are believed to depend on a suitable choice of solvent, the concentration of the substrate to be irradiated, and exact adherence to the period of irradiation. These parameters must be ascertained individually for each substrate.

The irradiation may be carried out with the full light of a Hg-high pressure lamp in a quartz glass apparatus. The temperature of the reaction solution may be, for example, approximately 25°C and the concentration of the solution preferably from 0.1 to 1.0 % by weight. Tetrahydrofuran and dioxan are preferably used as solvents, but it is also possible to use non-polar aprotic solvents, such, for example, as hexane, cyclohexane, benzene, toluene, and mixtures thereof. The period of irradiation is advantageously from 10 to 50 minutes.

A 13-epi-steroid of the general formula III or N-oxide or salt thereof may then be converted into a compound of the general formula I or N-oxide or salt thereof for example according to customary processes as described above, for example by nucleophilic addition to the 17-ketone, de-protection of the 3-ketone group and splitting off of water at the 4,5-position, and including, if desired, conversion of a radical represented by R^3 into another such radical and/or of a radical represented by R^4 into another such radical, at any suitable stage in the process.

Thus, for example, the process may include one or more of the following steps as appropriate:

(i) introduction of a group represented by R^3 of the general formula $-(CH_2)_nCH_3$ in which n represents 0 or an integer

X

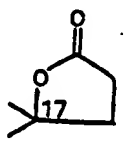
from 1 to 4 or $-(CH_2)_nCH_2CN$ where n represents 0 or an integer from 1 to 3 by an alkali metal-alkyl or alkali metal-alkylnitrile compound,

(ii) introduction of a group represented by R^3 of the general formula $-C\equiv CX$ in which X represents a hydrogen or halogen atom or an alkyl radical having from 1 to 4 carbon atoms, by means of a compound of the general formula $MC\equiv CX$ in which X has the meaning given above and M represents an alkali metal or by means of an alkali metal and a compound of the general formula $HC\equiv CX$ in which X has the meaning given above,

(iii) hydration of a triple bond in a group of the general formula $-C\equiv CH$ represented by R^3 to form a group of the group of the general formula $COCH_3$,

(iv) introduction of a group represented by R^3 of the general formula $-C\equiv C(CH_2)_nOR$ in which R represents a hydroxy-protecting group and n represents an integer from 1 to 4, by means of a compound of the general formula $MC\equiv C(CH_2)_nOR$ in which R and n have the meanings given above and M represents an alkali metal, and hydrogenating the resulting compound to form the corresponding hydroxyalkenyl or hydroxyalkyl radical of the general formula $-CH=CH-(CH_2)_nOH$ or $-CH_2CH_2(CH_2)_nOH$,

(v) oxidising a compound in which R^3 represents a 3-hydroxypropyl group and R^4 represents a hydroxy group to form, with the carbon atom to which they are attached, a group of the formula.



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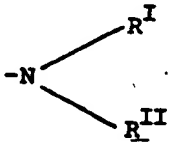
(vi) introducing a CH_2CN group represented by R^3 via formation of a spiro compound and splitting the spiro compound with HCN,

(vii) introducing a CH_2OH or $COCH_2OH$ group represented by R^3 by converting the 17-ketone to the corresponding 17- halo-17-alkoxycarbonyl compound, converting the halo group to an alkoxy group and reducing the 17-alkoxycarbonyl group to a CH_2OH group, and, if desired, converting the 17-alkoxy group to a 17-hydroxy group and also, if desired, converting the CH_2OH group to a $COCH_2OH$ group,

(viii) converting a hydroxy group represented by R^4 into an alkoxy or alkanoyloxy radical and/or converting a hydroxy group in a radical represented by R_3 into an alkoxy or alkanoyloxy radical,

(ix) converting a compound having a  group represented by R^1 into an acid addition salt thereof.

Nucleophilic addition at the C-17 position generally results in formation of both possible isomers; these are, however, readily separable by chromatography or fractional crystallisation. In many cases, both isomers are pharmacologically active, even though there may be differences in their strengths of action.

The nucleophilic addition of, for example, acetylene (ethyne) or propyne may be carried out using an agent that

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yields the radical -C≡CH or -C≡C-CH_3. Such agents are, for example, alkali metal acetylides, such as, for example, potassium and lithium acetylide or methylacetylide.

The organometallic compound may also be formed in situ and reacted with the 17-ketone of the general formula III. For example, acetylene and an alkali metal, especially potassium, sodium or lithium, may be made to act on the 17-ketone in a suitable solvent in the presence of an alcohol or in the presence of ammonia.

To introduce a 17-alkyl or 17-cyanoalkyl group, an alkali metal alkyl compound, for example methyl- or butyl-lithium, or alkali metal alkylnitrile, e.g. $Li(CH_2)_nCH_2CN$, may be used for reaction with the 17-ketone. Suitable solvents are, especially, dialkyl ethers, tetrahydrofuran, dioxan, benzene and toluene.

A 17-ethynyl-17-hydroxy compound may be hydrated in alcoholic solution with mercury salt catalysis to form a 17-acetyl-17-hydroxy compound (Chem. Ber. 111 (1978) 3086 - 3093).

A 3-hydroxypropyl or 3-hydroxypropenyl radical may be introduced into the 17-position by reacting the corresponding 17-ketone with a metallated derivative of propargyl alcohol, for example with 1-lithium 3-tetrahydropyran-2'-yloxyprop-1-yne, to form the 17-(3-hydroxyrop-1-ynyl)-17-hydroxy compound which is then hydrogenated to form the 17-(3-hydroxyropyl or 3-hydroxypropenyl)-17-hydroxy compound. The hydrogenation must be carried out under conditions that ensure that only the C-C triple bond is affected and that the tetrasubstituted 9(10)-double bond is not saturated. This is possible, for example, if the hydrogenation is carried out at room

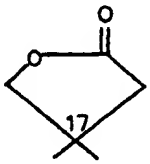
temperature and normal pressure in a solvent such, for example, as methanol, ethanol, propanol, tetrahydrofuran (THF) or ethyl acetate with the addition of a noble metal catalyst, such, for example, as platinum of palladium.

A compound with Z-configured double bond in the hydroxypropenyl group may be formed, for example, by hydrogenating the acetylenic triple bond with a deactivated noble metal catalyst (J. Fried, J.A. Edwards: Organic Reactions in Steroid Chemistry, Van Nostrand Reinhold Company 1972, page 134, and H.O. House: Modern Synthetic Reactions 1972, page 19). Suitable deactivated noble metal catalysts are, for example, 10 % palladium on barium sulphate in the presence of an amine or 5 % palladium on calcium carbonate with the addition of lead(II) acetate. The hydrogenation may be discontinued after the absorption of one equivalent of hydrogen.

A compound with E-configured double bond in the hydroxypropenyl group may be formed, for example, by reducing the acetylenic triple bond in a manner known per se. A whole series of methods for converting alkynes into trans-olefins are described in the literature, for example reduction with sodium in liquid ammonia (J. Am. Chem. Soc. 63 (1941) 216), with sodium amide in liquid ammonia (J. Chem. Soc. 1955, 3558), with lithium in low-molecular weight amines (J. Am. Chem. Soc. 77 (1955) 3378), with boranes (J. Am. Chem. Soc. 93 (1971) 3395 and 94 (1971) 6560), with diisobutylaluminium hydride and methyllithium (J. Am. Chem. Soc. 89 (1967) 5085) and especially with lithium aluminium hydride/alcoholate (J. Am. Chem. Soc. 89 (1967) 4245). A further possibility is the reduction of the triple bond with chromium(II) sulphate in the presence of water or dimethylformamide in weakly acidic medium (J. Am. Chem. Soc. 86 (1964) 4358) and generally

reduction by the action of transition metal compounds with a change in the oxidation stage.

If an end product in which CR^3R^4 represents



is desired, then a 17-(3-hydroxypropyl)-17-hydroxy compound may, for example, be oxidised in a manner known per se. The oxidation conditions generally depend on the nature of the substituent R^1 in formula I. If R^1 represents, for example, a dialkylamino group, then chromic acid reagents are generally unsuitable for oxidation since they attack primarily the dialkylamino group. In such cases an oxidation agent such, for example, as silver carbonate/Celite (a trade mark) (Fetizon reagent; M. Fetizon and M. Golfier, Compt. rend. 267 (1968) 900) or platinum/oxygen (H. Muxfeldt et al., Angewandte Chemie, Int. Ed. 1 (1962) 157) may be used. If, on the other hand, R^1 represents an alkoxy radical, it is also possible to use an oxidising agent such, for example, as Jones reagent, chromic acid-pyridine, pyridinium dichromate or pyridinium chlorochromate.

A 17-cyanomethyl side chain may be introduced, for example, in a manner known per se from the 17-ketone of the general formula III, for example via the 17-spiroepoxide and by cleaving the spiroepoxide with HCN according to Z. Chem. 18 (1978) 259 - 260.

The introduction of a 17-hydroxyacetyl side chain may also be carried out according to methods known per se, for

example according to the method described in J. Org. Chem. 47 (1982), 2993 - 2995.

If desired, a free hydroxy group represented by R^4 in the 17-position may be esterified or etherified, for example, in a manner known per se. Similarly, a free hydroxy or mercapto group in the radical represented by R^3 may, if desired, be etherified or esterified.

Splitting off of water, with the formation of the 4(5)-double bond, and simultaneous cleavage of the ketal group in the 3-position (and removal of any other protecting groups present that can be split off with acid) may be effected with acid or an acidic ion exchanger.

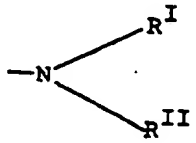
The acid treatment may be carried out in a manner known per se. For example, the compound of the general formula IV which contains a 3-ketal group and a 5α-hydroxy group (and, in some cases, an optionally O-protected 17-hydroxy group and/or hydroxy-substituted 17-aliphatic hydrocarbon radical) is dissolved in a water-miscible solvent, e.g. aqueous methanol, ethanol or acetone, in the presence of a catalytic quantity of a mineral or organic, e.g. sulphonic, acid, e.g. hydrochloric acid, sulphuric acid, phosphoric acid, perchloric acid, p-toluenesulphonic acid or acetic acid, until water has been split off and protecting group(s) have been removed. The reaction, which generally proceeds at a temperature of from 0 to 100°C, may also be carried out with an acidic ion exchanger. The course of the reaction may be followed by analytical methods, for example by thin layer chromatography of samples taken.

The 13α-alkylgonanes of the general formula I and their N-oxides and physiologically tolerable salts may be used in

the form of pharmaceutical preparations. The preparations may be prepared, for example, according to methods of galenical pharmacy known per se by mixing with organic or inorganic inert carrier material suitable for enteral, percutaneous or parenteral administration.

In the case of human beings, the dosage of the active ingredients according to the invention may be, for example, from 10 to 1000 mg per day.

Thus, the present invention provides a pharmaceutical preparation which comprises a compound of the general formula I or an N-oxide or physiologically tolerable acid addition salt of such compound in which R^1 represents a group of the general formula



in admixture or conjunction with a pharmaceutically suitable carrier. Preferably, the pharmaceutical preparation is in dosage unit form containing, for example, 10 to 100 mg of active ingredient per dosage unit.

The following Examples illustrate the invention.

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Examples

A. Preparation of compounds of the invention

Example 1

a) A solution of 2.0 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-9(10)-oestren-17-one (m.p. 143-145°C) in 300 ml of absolute tetrahydrofuran (THF) is irradiated for 16 minutes at 25°C with a Hg-high pressure lamp (Philips HPK 125, immersion lamp, quartz glass reactor). The solvent is then distilled off in vacuo and the residue is chromatographed over aluminium oxide (Merck, neutral, stage III) with hexane/ethyl acetate. 1.46 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9(10)-gonen-17-one are obtained in the form of a colourless oil.

b) At 5°C, absolute THF (248 ml) is saturated with acetylene by introducing the latter over a period of 30 minutes. 51 ml of a 15 % solution of n-butyllithium in hexane are then slowly added dropwise and the whole is stirred for a further 15 minutes while cooling with ice-water. A solution of 2.7 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one in 40 ml of absolute THF is then added dropwise over a period of 15 minutes to the suspension of the lithium acetylide and stirring is carried out for a further 2 hours at room temperature. For working up, the whole is poured into ice-water and extracted with ethyl acetate. The resulting crude product (2.85 g) is used in the following stage without being further purified.

X

c) 2.8 g of the crude product obtained under b) are suspended in 29 ml of 70 % aqueous acetic acid and stirred for 3 hours at 50°C. After cooling, the suspension is diluted with approximately 100 ml of water and adjusted to a pH of 10.5 by adding concentrated aqueous NH_3 solution. After extracting with ethyl acetate, an oily mixture of isomers is obtained that is separated by column chromatography over silica gel with hexane/ethyl acetate. There are obtained in the order of elution:

1. 530 mg of 11β-(4-dimethylaminophenyl)-17α-ethynyl-17β-hydroxy-13β-methyl-4,9-gonadien-3-one having a melting point of 120 - 123°C (ethyl acetate/diisopropyl ether) and

2. 1.33 g of 11β-(4-dimethylaminophenyl)-17β-ethynyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one having a melting point of 201 - 204°C (ethyl acetate).

Analogously to b) and c), there are obtained using methylacetylene instead of acetylene:

1. 11β-(4-dimethylaminophenyl)-17β-hydroxy-13α-methyl-17α-propynyl-4,9-gonadien-3-one in the form of an oil.

2. 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-17β-propynyl-4,9-gonadien-3-one in the form of an oil.

d) After the addition of 0.87 ml of concentrated sulphuric acid, a suspension of 1.02 of mercury oxide (HgO, red) in 20 ml of water is stirred for 30 minutes at 60°C. 9 ml of this mercury salt solution are added to a solution of 3.25 g of 11β-(4-dimethylaminophenyl)-17β-ethynyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one in 32 ml of glacial acetic acid.

X

The whole is then stirred for 2 hours at 60°C. For working up, the cooled reaction solution is poured into ice-water, adjusted to a pH of 10.5 by adding concentrated aqueous NH_3 solution and extracted with ethyl acetate. The resulting oily crude product is crystallised from methylene chloride/diisopropyl ether. 2.37 g of 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione having a melting point of 224 - 225°C are obtained.

e) A suspension of 2.3 g of 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione in 58 ml of toluene is stirred for 20 hours at 25°C after the addition of 11.6 ml of acetic anhydride and 5.8 g of 4-dimethylaminopyridine. The suspension is then poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate. The crude product is chromatographed over 200 g of silica gel with hexane/ethyl acetate. After crystallising the main fraction from hexane/ethyl acetate, 1.71 g of 17α-acetoxy-11β-(4-dimethylaminophenyl)-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione having a melting point of 194 - 195°C are obtained.

Example 2

a) A solution of 1.8 g of 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-9-oestren-17-one (m.p. 223 - 226°C) in 300 ml of THF are irradiated for 26 minutes under the conditions of Example 1 a). After chromatography of the crude product, 1.58 g of 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one are obtained in the form of a colourless oil.

X

b) At 0°C, the organo-lithium compound is prepared from 3.94 g of 3-tetrahydropyran-2'-yloxy-1-propyne in 85 ml of absolute THF and 23.1 of a 15 % solution of n-butyl-lithium in hexane. A solution of 3.53 g of the product described under 2 a) in 71 ml of absolute THF is then added dropwise and the whole is stirred for 4 hours at room temperature. The reaction solution is afterwards poured into ice-water and extracted with ethyl acetate. The crude product (3.85 g) of 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17α-[3-(tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α,17β-diol and 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17β-[3-(tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α,17α-diol is used for hydrogenation without being further purified.

c) After the addition of 400 mg of 10 % palladium/carbon, 3.85 g of the crude product obtained under 2 b) are hydrogenated in 95 ml of ethanol at room temperature and normal pressure. After 191 ml of hydrogen have been taken up, the catalyst is filtered off and concentration is carried out.

d) The crude hydrogenation product (3.85 g) obtained under 2 c) is stirred in 30 ml of 70 % acetic acid for 2 hours at 60°C. After cooling, working-up is carried out as under 1 c) and the resulting mixture of isomers is chromatographed. There are obtained in the order of elution:

1. 410 mg of 11β-(4-diethylaminophenyl)-17α-(3-hydroxy-propyl)-17β-hydroxy-13α-methyl-4,9-gonadien-3-one in the form of a yellowish oil.

   UV (methanol): $\epsilon_{266} = 19080, \epsilon_{309} = 19110$.

X

2. 1.39 g of 11β-(4-diethylaminophenyl)-17β-(3-hydroxypropyl)-17α-hydroxy-13α-methyl-4,9-gonadien-3-one in the form of a solid foam.

Analogously to b) to d), there are obtained when using 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one as starting material:

1.) 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one in the form of an oil.

2.) 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one in the form of an oil.

Example 3

a) A solution of 1.75 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-11β-(4-methoxyphenyl)-9-oestren-17-one in 290 ml of dioxan is irradiated for 19 minutes under the conditions of Example 1 a). After chromatography, 1.45 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-11β-(4-methoxyphenyl)-13α-methyl-9-gonen-17-one are obtained in the form of a colourless oil.

b) A solution of 8.2 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-11β-(4-methoxyphenyl)-13α-methyl-9-gonen-17-one in 130 ml THF is added dropwise to a suspension of lithium acetylide prepared from a saturated solution of acetylene in 450 ml of THF and 130 ml of a 15 % solution of n-butyllithium in hexane. Sitrring is then carried out for 3 hours at room temperature and the reaction solution is

X

afterwards poured into approximately 3 l of ice-water and extracted with ethyl acetate. The crude product is chromatographed over aluminium oxide with hexane/ethyl acetate. There are obtained in the order of elution:

1. 1.8 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-17α-ethynyl-11β-(4-methoxyphenyl)-13α-methyl-9-gonen-5α,17β-diol in the form of a colourless oil.

2. 5.1 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-17β-ethynyl-11β-(4-methoxyphenyl)-13α-methyl-9-gonene-5α,17α-diol in the form of a solid foam.

c) A solution of 3.28 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-17β-ethynyl-11β-(4-methoxyphenyl)-13α-methyl-9-gonene-5α,17α-diol in 33 ml of 70 % aqueous acetic acid is stirred for 30 minutes at 60°C. After cooling, the solution is poured into ice-water and extracted with methylene chloride and the $MeCl_2$ extracts are washed with saturated $NaHCO_3$ solution and concentrated. Crystallisation of the crude product from ethyl acetate yields 2.0 g of 17β-ethynyl-17α-hydroxy-11β-(4-methoxyphenyl)-13α-methyl-4,9-gonadien-3-one having a melting point of 186 - 187°C.

Example 4

a) 20 minutes' irradiation of 1.84 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-18-methyl-9-oestren-17-one in 280 ml of THF under the conditions of Example 1 a) results in 1.36 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-ethyl-5α-hydroxy-9-gonen-17-one in the form of a foam.

X

b) 6.1 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-ethyl-5α-hydroxy-9-gonen-17-one are reacted under the conditions of Example 1 b) with lithium acetylide and the resulting crude product is cleaved with acetic acid under the conditions of Example 1 c). After chromatography and crystallisation from ethyl acetate/diisopropyl ether, 3.2 g of 11β-(4-dimethylaminophenyl)-17β-ethynyl-13α-ethyl-17α-hydroxy-4,9-gonadien-3-one having a melting point of 197 - 198°C are obtained.

$[\alpha]_D^{25}$ + 450.4° ($CHCl_3$, c = 0.505).

c) By hydration, catalysed with mercury salt, analogous to Example 1 d) and subsequent acetylation analogous to Example 1 e), there are obtained from 1.3 g of 11β-(4-dimethylaminophenyl)-17β-ethynyl-13α-ethyl-17α-hydroxy-4,9-gonadien-3-one, after chromatographic purification, 720 mg of 17α-acetoxy-11β-(4-dimethylaminophenyl)-13α-ethyl-18,19-dinor-4,9-pregnadiene-3,20-dione in the form of a solid foam.

$[\alpha]_D^{25}$ + 290.8° ($CHCl_3$, c = 0.515).

X

Example 5

a) By reacting 7.3 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one with 10.7 g of 3-tetrahydropyran-2'-yloxy-1-propyne under the conditions of Example 2 b) there are obtained, after chromatography of the crude product over aluminium oxide with hexane/ethyl acetate, 4.83 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17β-[3-(tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α,17α-diol in the form of a yellowish foam.

b) After the addition of 210 mg of palladium on barium sulphate (10 %), a solution of 2.2 g of the adduct obtained under a) in 67 ml of ethanol and 0.56 ml of triethylamine is hydrogenated at room temperature and normal pressure. After 83.5 ml of hydrogen have been taken up, the catalyst is filtered off and concentrated. The resulting crude hydrogenation product is cleaved with 14 ml of 70 % acetic acid under the conditions of Example 1 c). After crystallisation from ethyl acetate/diisopropyl ether, 1.1 g of 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxy-1(Z)-propenyl)-13α-methyl-4,9-gonadien-3-one having a melting point of 133 - 135°C are obtained.

X

Example 6

Manufacture of 11β-(4-dimethylaminophenyl)-17β-ethynyl-16β-ethyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one

a) A suspension of 29.3 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5(10),9(11)-oestradien-17-one and 28.6 g of bis-dimethylamino-tert.-butoxymethane is stirred under argon for 60 minutes at 160°C. After cooling, the crude product is triturated with approximately 50 ml of ethyl acetate, filtered, and the filtration residue is recrystallised from ethyl acetate. In this manner, 27.6 g of 16-dimethylaminomethylene-3,3-(2,2-dimethylpropane-1,3-dioxy)-5(10),9(11)-oestradien-17-one having a melting point of 208 - 211°C are obtained.

b) 85 ml of a 5 % solution of methyllithium in diethyl ether are added dropwise while cooling with ice-water to a solution of 14.4 g of 16-dimethylaminomethylene-3,3-(2,2-dimethylpropane-1,3-dioxy)-5(10),9(11)-oestradien-17-one in 220 ml of toluene. When the addition is complete, the whole is stirred for 15 minutes at +5 to +10°C, excess reagent is decomposed by the careful addition of approximately 20 ml of water and the reaction solution is then poured into approximately 3 l of ice-water and extracted with methylene chloride. The crude product is chromatographed over neutral

X

aluminium oxide with hexane/ethyl acetate. After crystallisation of the main fraction from ethyl acetate, 13.0 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-16(E)-ethylidene-5(10),9(11)-oestradien-17-one having a melting point of 121 - 123°C are obtained.

c) 4.3 ml of 30 % hydrogen peroxide are added dropwise while cooling with ice-water to a solution of 9.4 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-16(E)-ethylidene-5(10),9(11)-oestradien-17-one in 43 ml of methylene chloride, 0.34 ml of hexachloroacetone and 0.01 ml of pyridine and then the whole is stirred for 16 hours at 25°C. For working up, the reaction solution is diluted with approximately 100 ml of methylene chloride and washed in succession with 5 % $Na_2S_2O_3$ solution and water; the methylene chloride phase is dried over Na_2SO_4 and concentrated. The resulting 5,10-epoxide mixture is chromatographed over Al_2O_3, neutral, stage III, with hexane/ethyl acetate. 4.7 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α,10α-epoxy-16(E)-ethyliden-9(11)-oestren-17-one having a melting point of 139 - 141°C (ethyl acetate/diisopropyl ether) are obtained.

X

d) After the addition of 930 mg of palladium/carbon (10 %), a solution of 8.2 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α,10α-epoxy-16(E)-ethyliden-9(11)-oestren-17-one in 400 ml of ethanol is hydrogenated at room temperature and normal pressure. After 510 ml of hydrogen have been taken up, the catalyst is filtered off and concentration is carried out in vacuo. 7.7 g of 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α,10α-epoxy-16β-ethyl-9(11)-oestren-17-one are obtained in the form of a colourless oil.

e) An organo-magnesium compound is prepared from 1.4 g of magnesium, 0.05 ml of methyl iodide and 17.9 g of 4-bromo-N,N-dimethylaniline in 150 ml of absolute THF. After the addition of 344 g of CuCl, the whole is stirred for 15 minutes at 0°C and a solution of 7.7 g of the product obtained under d) in 70 ml of absolute THF is then added dropwise. Afterwards, the whole is stirred for 3.5 hours at room temperature. For working up, the reaction solution is poured into a mixture of ice-water and NH_3 solution and extracted with ethyl acetate. After chromatography of the crude product over aluminium oxide with hexane/ethyl acetate and crystallisation of the main fraction from diisopropyl ether/ethyl acetate, 6.5 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-16β-ethyl-5α-hydroxy-9(10)-oestren-17-one having a melting point of 180 - 181°C are obtained.

X

f) A solution of 4.0 g of the product obtained under e) in 600 ml of dioxan is irradiated under the conditions of Example 1 a). After crystallisation of the crude irradiation product from diisopropyl ether, 1.74 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-16β-ethyl-5α-hydroxy-13α-methyl-9(10)-gonen-17-one having a melting point of 192 - 194°C are obtained.

g) 1.4 g of the product obtained under f) are reacted with lithium acetylide under the conditions of Example 1 b). After crystallisation of the crude product from ethyl acetate/diisopropyl ether, 960 mg of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-17β-ethynyl-16β-ethyl-13α-methyl-9(10)-gonene-5α,17α-diol having a melting point of 132 - 134°C are obtained.

h) 760 mg of the product obtained under g) are reacted with 8 ml of 70 % acetic acid under the conditions of Example 1 c). Crystallisation of the crude product from hexane/diethyl ether yields 460 mg of 11β-(4-dimethylaminophenyl)-17β-ethynyl-16β-ethyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one having a melting point of 195 - 197°C.

X

Example 7

Manufacture of 17β-cyanomethyl-11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-4,9-gonadien-3-one

a) 2.63 g of potassium tert.-butoxide are added in portions, while cooling with ice-water, to a suspension of 5.0 g of 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9(10)-gonen-17-one and 4.74 of trimethylsulphonium iodide in 60 ml of dimethylformamide. The whole is stirred for 4 hours at 25°C, then poured into ice-water and extracted with ethyl acetate. After removing the solvent, the crude product, which is at first oily, is crystallised from ethyl acetate/diisopropyl ether and, in this manner, 4.2 g of 11β-(4-dimethylamino-phenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9(10)-gonene-17α-spiro-1',2'-oxirane having a melting point of 234 - 236°C are obtained.

X

b) 2.0 g of the spiro-oxirane obtained under a) are dissolved in 84 ml of ethanol and, after the addition of 4.6 g of potassium cyanide, the whole is heated under reflux for 4 hours. The cooled solution is poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate. The crude product obtained after concentration is taken up in 26 ml of 70 % acetic acid without being further purified and stirred for 60 minutes at 60°C. After cooling, the whole is poured into ice-water, adjusted to a pH of 10.5 by adding NH_3 solution and extracted with methylene chloride. After chromatography of the crude product over silica gel with hexane/acetone and crystallisation of the main fraction from ethanol, 1.4 g of 17β-cyanomethyl-11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-4,9-gonadien-3-one having a melting point of 135 - 137°C are obtained.

X

B. Tests on antigestagenic action

In order to identify the antigestagenic action of the compounds according to the invention, the abortive action was investigated at an early stage post nidationem (Experiment I) and at an advanced stage post nidationem (Experiment II).

The experiments were carried out on female rats weighing approximately 200 g. After mating had taken place, the commencement of pregnancy was ascertained by the detection of spermatozoa in vaginal smears. The day on which sperm was detected is designated day 1 of gravidity (= d 1 p.c.).

The following were investigated for antigestagenic action:

A: 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-propynyl-4,9-oestradien-3-one (reference substance).

B: 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one (compound of the invention).

C: 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one (compound of the invention).

The test substances were dissolved in a mixture of benzyl benzoate and castor oil (ratio 1:4). The volume of vehicle per individual dose was 0.2 ml. The treatment was carried out subcutaneously (s.c.).

The treatment of the animals with the particular substance to be tested or with the solvent as control was carried out after the nidation of the blastocysts from day 5 p.c. to day 7 p.c. (Experiment I) and day 13 p.c. to day 15 p.c. (Experiment II). On day 9 p.c. and day 17 p.c., respectively, the animals were killed and the uteri were examined for implants and absorption sites. Photographs were taken of all the uteri. The lack of implants was assessed as abortion.

The results are given in Tables 1 and 2 below.

Compounds B and C of the general formula I of the invention had a completely abortive action in rats at an early stage of pregnancy in doses $\geq$ 1.0 mg/day (abortion rate: 4/4). In contrast, the reference substance A exhibited maximum abortion-inducing (antigestagenic) action only at doses of $\geq$ 3.0 mg/day (Table 1).

At an advanced stage of pregnancy (day 13 to 15 p.c.), the percentage of complete abortions with s.c. administration for 3 days of 3.0 mg/day was 35.4 % for B, 52.3 % for C and 3.5 % for the comparison substance A (Table 2).

Table 1 (Experiment I)

Abortive action at an early stage of pregnancy in rats

Treatment from d 5 p.c. to d 7 p.c., autopsy d 9 p.c.

compound	dose mg/animal/day s.c.	rate of abortion n abortion/n total (%)
A	30.0	4/4 (100)
	10.0	- -
	3.0	4/4 (100)
	1.0	2/4 (50)
	0.3	0/4 (0)
	0.1	0/4 (0)
B	10.0	4/4 (100)
	3.0	4/4 (100)
	1.0	4/4 (100)
	0.3	0/4 (0)
	0.1	0/4 (0)
C	10.0	4/4 (100)
	3.0	4/4 (100)
	1.0	4/4 (100)
	0.3	0/4 (0)
	0.1	0/4 (0)
solvent as control: 0.2 ml benzyl benzoate + castor oil (1 : 4)	-	0/4 (0)

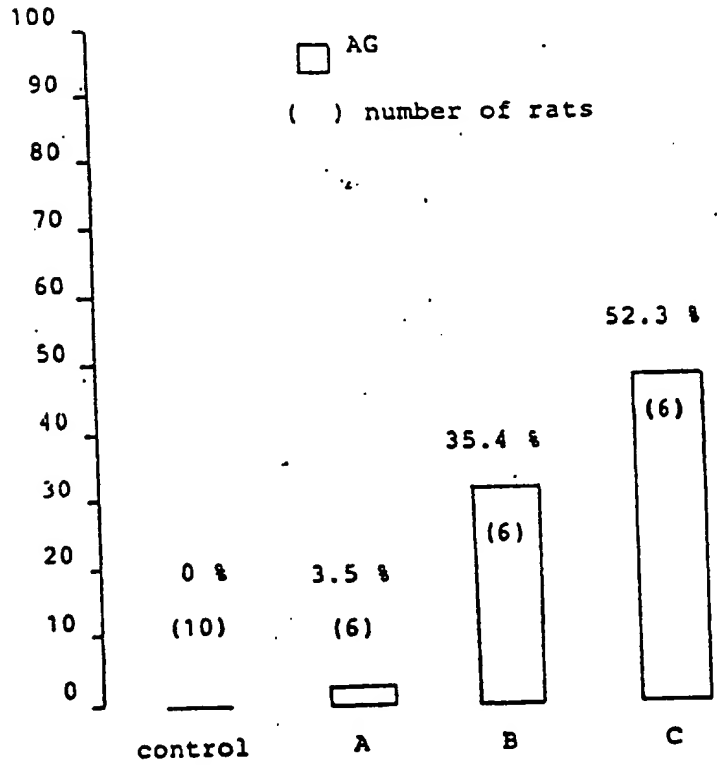
n = 4 rats/group

Table 2 (Experiment II)

Abortive action at an advanced stage of pregnancy in rats

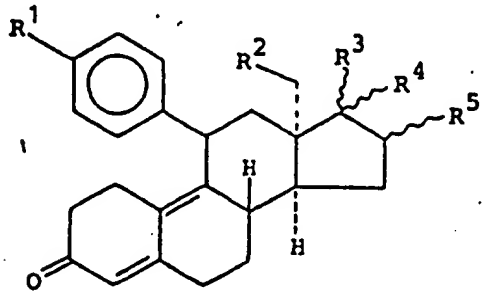
Treatment with 3.0 mg/d s.c. antigestagen (AG) from d 13 p.c. to d 15 p.c., autopsy d 17 p.c.

% complete abortions
= empty nidation sites



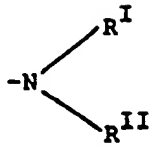
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of the general formula



(I)

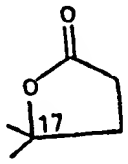
in which R^1 represents a group of the general formula



in which R^I and R^{II}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, or R^I and R^{II}, together with the nitrogen atom to which they aretached,represent a saturated 5- or 6-membered ring, which may contain a further hereto atom, or a corresponding tertiary N-oxide group, or OR^{III} in which R^{III} represents a methyl, ethyl, propyl, isopropyl, methoxyphenyl, allyl or β-dimethylaminoethyl group, R^2 represents a hydrogen atom, a methyl group or an ethyl group, R^3 represents a group of the general formula $-(CH_2)_n-CH_3$ in which n represents 0 or an integer from 1 to 5, a group of the general formula $-(CH_2)_n-CH_2-OR^{IV}$ or $-(CH_2)_n-CH_2-SR^{IV}$ in which n represents 0 or an integer from 1 to 4, and R^{IV} represents a hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms, a group of the general formula $-CH=CH-(CH_2)_n-OR^V$ in which n represents an integer from 1 to 4, and R^V represents a

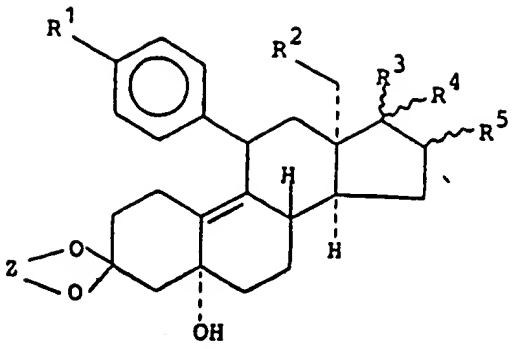
B

hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms, a group of the general formula $-C\equiv C-X$ in which X represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms or a halogen atom, a group of the general formula $-(CH_2)_n-CH_2CN$ in which n represents 0 or an integer from 1 to 3, or a group of the formula $-\overset{O}{\overset{\|}{C}}-CH_2Y$ in which Y represents a hydrogen atom or a group of the general formula OR^V in which R^V has the meaning given above+, R^4 represents a hydroxy group or an alkoxy or alkanoyloxy radical each having from 1 to 4 carbon atoms or R^3 and R^4, together with the carbon atom to which they are attached, represent a group of the formula

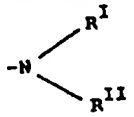


and R^3 is in the α-configuration and R^4 is in the β-configuration or R^3 is in the β-configuration and R^4 is in the α-configuration with respect to the steroid structure, and R^5 represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms and being in the α- or β-configuration or a pharmaceutically acceptable acid addition salt of such a compound in which R^1 represents a group of the general formula $-N\begin{matrix}R^1\\R^{II}\end{matrix}$, which comprises (a) cleaving the 3-ketal protecting group and splitting off water from the 4,5-position in a compound of the general formula

B,

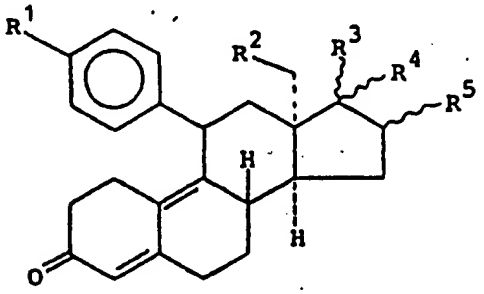


IV

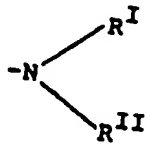
in which R^1, R^2, R^3, R^4 and R^5 have the meanings given above and Z represents a ketone-protecting group, or an acid addition salt of such a compound in which R^1 represents a group of the general formula  .

2. A process as claimed in claim 1, wherein Z is an ethylene or 2,2-dimethylpropylene group.

3. A compound of the general formula

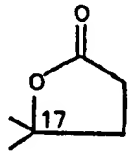


(I)

in which R^1 represents a group of the general formula 

in which R^I and R^{II}, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, or R^I and R^{II}, together with the nitrogen atom to which they are attached, represent a saturated 5- or 6-membered ring, which may contain a further hetero atom, or a corresponding tertiary N-oxide group, or OR^{III} in which R^{III} represents a methyl, ethyl, propyl, isopropyl, methoxyphenyl, allyl or β-

dimethylaminoethyl group, R^2 represents a hydrogen atom, a methyl group or an ethyl group, R^3 repres nts a group of the general formula $-(CH_2)_n-CH_3$ in which n repres nts 0 or an int ger from 1 to 5, a group of the general formula $-(CH_2)_n-OR^{IV}$ or $-(CH_2)_n-CH_2-SR^{IV}$ in which n represents 0 or an integer from 1 to 4, and R^{IV} represents a hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms, a group of the general formula $-CH=CH-(CH_2)_n-OR^V$ in which n represents an integer from 1 to 4, and R^V represents a hydrogen atom or an alkyl or alkanoyl radical each having from 1 to 4 carbon atoms, a group of the general formula $-C\equiv C-X$ in which X represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms or a halogen atom, a group of the general formula $-(CH_2)_n-CH_2CN$ in which n represents 0 or an integer from 1 to 3, or a group of the formula $-\overset{O}{\overset{\|}{C}}-CH_2Y$ in which Y represents a hydrogen atom of a group of the general formula OR^V in which R^V has the meaning given above, R^4 represents a hydroxy group or an alkoxy or alkanoyloxy radical each having from 1 to 4 carbon atoms or R^3 and R^4, together with the carbon atoms to which they are attached, represent a group of the formula



and R^3 is in the α-configuration and R^4 is in the β-configuration or R^3 is in the β-configuration and R^4 is in the α-configuration with respect to the steroid structure, and R^5 represents a hydrogen atom or an alkyl radical having from 1 to 4 carbon atoms and being in the α- or β-configuration of a pharmaceutically acceptable acid addition salt thereof.

4. A process as claimed in claim 1, wherein R^1 represents $N(CH_3)_2$, $N(C_2H_5)_2$ or OCH_3.

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5. A compound of formula I giv n in claim 1, wherein R^2 through R^5 are as in claim 1 and R^1 repres nts $N(CH_3)_2$, $N(C_2H_5)_2$ or OCH_3 or a pharmaceutically acceptable acid addition salt thereof.

6. A process as claimed in claim 4, in which R^2 is hydrogen or methyl.

7. A compound of formula I given in claim 1, in which R^1 is as in claim 4, R^2 is as in claim 6 and R^3 through R^5 are as in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

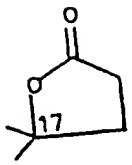
8. A process as claimed in claim 6, wherein R^3 represents $C{\equiv}CH$, $C{\equiv}CCH_3$, CH_2CH_2OH, $CH{=}CHCH_2OH$, CH_2CH or $COCH_3$.

9. A compound of formula I given in claim 1, wherein R^1 is as in claim 4, R^2 is hydrogen or methyl, R^3 is as in claim 8 and R^4 and R^5 are as in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

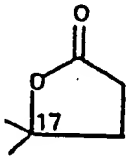
10. A process as claimed in claim 8, wherein R^4 represents OH or, when R^3 represents $COCH_3$, R^4 represents $OCOCH_3$.

11. A compound of formula I given in claim 1, wherein R^1 is as in claim 4, R^2 is hydrogen or methyl, R^3 represents $C{\equiv}CH$, $C{\equiv}CCH_3$, CH_2CH_2OH, $CH{=}CHCH_2OH$, CH_2CN or $COCH_3$ and R^4 is as in claim 10 and R^5 is as in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

12. A process as claimed in claim 8, wherein R^3 and R^4 together with the carbon atom to which they are attached represent a group of the formula



13. A compound of formula I giv n in claim 1, wh rein R^3 and R^4, together with the carbon atom to which they are attached, represent a group of the formula



R^1 is as in claim 4, R^2 is hydrogen or methyl and R^5 is as in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

14. A process as claimed in claim 10, wherein R^5 represents H or C_2H_5.

15. A compound of formula I given in claim 1, wherein R^I is as in claim 4, R^2 is hydrogen or methyl, R^3 represents $C{\equiv}CH$, $C{\equiv}CCH_3$, CH_2CH_2OH, $CH{=}CHCH_2OH$, CH_2CN or $COCH_3$, R^4 represents $OCOCH_3$ and R^5 is as in claim 14 or a pharmaceutically acceptable acid addition salt thereof.

16. A process as claimed in claim 12, wherein R^5 represents H or C_2H_5.

17. A compound of formula I given in claim 1, wherein R^1 is as in claim 4, R^2 is hydrogen or methyl, R^3 represents $-C{\equiv}CH$, $-C{\equiv}CCH_3-$, $-CH_2CH_2OH-$, $-CH{=}CHCH_2OH$, $-CH_2CN$ or $COCH_3$, R^3 and R^4, together with the carbon atom to which they are attached, represent a group of the formula

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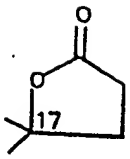

and R^5 is as in claim 16 or a pharmaceutically acc ptable acid addition salt thereof.

18. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-9(10)-oestren-17-one in absolute tetrahydrofuran reacting the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one obtained in absolute tetrahydrofuran with a lithium acetylide suspension in absolute tetrahydrofuran and treating the product obtained with aqueous acetic acid, and after dilution with water concentrated aqueous NH_3, and the isomer mixture obtained is separated by column chromatography.

19. 11β-(4-dimethylaminophenyl)-17α-ethynyl-17β-hydroxy-13α-methyl-4,9-gonadien-3-one.

20. 11β-(4-dimethylaminophenyl)-17β-ethynyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one.

21. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-9(10)-oestren-17-one in absolute tetrahydrofuran reacting the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one obtained in absolute tetrahydrofuran with a lithium methyl acetylide suspension in absolute tetrahydrofuran, and treating the product obtained with aqueous acetic acid, and after dilution with water concentrated aqueous NH_3 and the isomer mixture obtained is separated by column chromatography.

22. 11β-(4-dimethylaminophenyl)-17β-hydroxy-13α-

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methyl-17α-propynyl-4,9-gonadi n-3-one.

23. 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-17β-propynyl-4,9-gonadien-3-one.

24. A process as claimed in claim 21, in which the 11β-(4-dimethylaminophenyl)-17β-ethynyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one obtained in glacial acetic acid is treated with a mercury salt solution obtained by the addition of a suspension of mercury oxide in water to concentrated sulphuric acid.

25. 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione.

26. A process as claimed in claim 24, in which the 11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione obtained is reacted in toluene with acetic anhydride and 4-dimethylaminopyridine.

27. 17α-acetoxy-11β-(4-dimethylaminophenyl)-13α-methyl-18,19-dinor-4,9-pregnadiene-3,20-dione.

28. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-9-oestran-17-one in absolute tetrahydrofuran, and reacting the 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one obtained in absolute tetrahydrofuran with a solution of an organo-lithium compound prepared by adding 3-tetrahydropyran-2'-yloxy-1-propyne in absolute tetrahydrofuran to n-butyl-lithium in hexane, hydrogenating the 11β-(4-diethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17α-[3-tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α,17β-diol and 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17β-[3-(tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α, 17α-diol obtained in ethanol in the presence of palladium/carbon,

treating the crude product obtained with acetic acid and s parating the isomer by chromatography.

29. 11β-(4-diethylaminophenyl)-17α-(3-hydroxypropyl)-17β-hydroxy-13α-methyl-4,9-gonadien-3-one.

30. 11β-(4-diethylaminophenyl)-17β-(3-hydroxypropyl)-17β-hydroxy-13α-methyl-4,9-gonadien-3-one.

31. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one in absolute tetrahydrofuran, reacting the product obtained in absolute tetrahydrofuran with a solution of an organo-lithium compound prepared by adding 3-tetrahydropyran-2'-yloxy-1-propyne in absolute tetrahydrofuran to n-butyl-lithium in hexane; hydrogenating the product obtained in ethanol in the presence of palladium-carbon, treating the crude product obtained with acetic acid and separating the isomers by chromatography.

32. 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one.

33. 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-13α-methyl-4,9-gonadien-3-one.

34. A process which comprises irradiating 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-11β-(4-methoxyphenyl)-9-oestren-17-one in dioxane, reacting the 3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-11β-(4-methoxyphenyl)-13α-methyl-9-gonen-17-one obtained in absolute tetrahydrofuran with a suspension of lithium acetylide in absolute tetrahydrofuran, chromatographing the product obtained, and treating the 3,3-(2,2-dimethylpropane-1,3-hydroxy-17β-ethynyl-11β-(4-methoxyphenyl)-13α-methyl-9-gonene-5α,17α-diol obtained with aqueous acetic acid.

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35. 17β-ethynyl-17α-hydroxy-11β-(4-methoxyphenyl)-13α-methyl-4,9-gonadien-3-one.

36. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-18-methyl-9-oestren-17-one in absolute tetrahydrofuran reacting the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-ethyl-5α-hydroxy-9-gonen-17-one obtained in absolute tetrahydrofuran with a lithium acetylide suspension in absolute tetrahydrofuran and treating the product obtained with aqueous acetic acid and after dilusion with water concentrated aqueous NH_3, and the isomer mixture obtained is separated by column chromatography.

37. 11β-(4-dimethylaminophenyl)-17β-ethynyl-13α-ethyl-17α-hydroxy-4,9-gonadien-3-one.

38. A process as claimed in claim 36, in which the 11β-(4-dimethylaminophenyl)-17β-ethynyl-13α-ethyl-17α-hydroxy-4,9-gonadien-3-one obtained in glacial acetic acid is treated with a mercury salt solution obtained by the addition of a suspension of mercury oxide in water to concentrated sulphuric acid.

39. 17α-acetoxy-11β-(4-dimethylaminophenyl)-13α-ethyl-18,19-dinor-4,9-pregnadiene-3,20-dione.

40. A process which comprises reacting 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9-gonen-17-one in absolute tetrahydrofuran with a solution of an organo-lithium compound prepared by adding 3-tetrahydropyran-2'-yloxy-1-propyne in absolute tetrahydrofuran to n-butyl-lithium in hexane, hydrogenating the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-13α-methyl-17β-[3-tetrahydropyran-2-yloxy)-1-propynyl]-9-gonene-5α,17α-diol obtained in ethanol in the presence of triethylamine and palla-

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dium or boron sulphate and treating the product obtained with acetic acid.

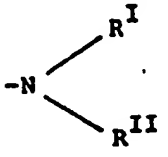
41. 11β-(4-dimethylaminophenyl)-17α-hydroxy-17β-(3-hydroxy-1(Z)-propenyl)-13α-methyl-4,9-gonadien-3-one.

42. A process which comprises irradiating 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-16β-ethyl-5α-hydroxy-9(10)-oestren-17-one in absolute tetrahydrofuran reacting the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-16β-ethyl-5α-hydroxy-13α-methyl-9(10)-gonen-17-one obtained in absolute tetrahydrofuran with a lithium acetylide suspension in absolute tetrahydrofuran and treating the product obtained with aqueous acetic acid, and after dilution with water concentrated aqueous NH_3 and the isomer mixture obtained is separated by column chromatography.

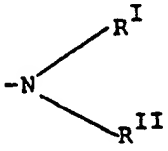
43. 11β-(4-dimethylaminophenyl)-17β-ethynyl-16β-ethyl-17α-hydroxy-13α-methyl-4,9-gonadien-3-one.

44. A process which comprises reacting 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9(10)-gonen-17-one, trimethylsulphonium iodide and potassium tert.-butoxide in dimethyl formamide and heating the 11β-(4-dimethylaminophenyl)-3,3-(2,2-dimethylpropane-1,3-dioxy)-5α-hydroxy-13α-methyl-9(10)-gonen-17α-spiro-1',2'-oxirane obtained in ethanol with potassium cyanide.

45. 17β-cyanomethyl-11β-(4-dimethylaminophenyl)-17α-hydroxy-13α-methyl-4,9-gonadien-3-one.

46. A process as claimed in claim 1, which comprises converting a compound of the general formula I in which R_1 represents a group of the general formula  wherein

R^I and R^{II} are as in claim 1 into a pharmaceutically acceptable acid addition salt.

47. A physiologically tolerable acid addition salt of a compound of the general formula I in which R_1 represents a group of the formula  wherein R^I and R^{II} are as in claim 1.

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